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| 09/412,268 | 10/05/1999 | BEHNAZ PARHAMI-SEREN | MGH-1526 | 9455 |

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EXAMINER

UNGAR, SUSAN NMN

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1642

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HC

Office Action Summary

Application No.

09/412,268

Applicant(s)

PARHAMI-SEREN ET AL.

Examiner

Susan Ungar

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 11 April 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above claim(s) 7-37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-6 and 38-60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to you 37 CFR 1.114. Applicant's submission filed April 11, 2005 is acknowledged and has been entered.
2. The Amendment filed April 11, 2005 in response to the Office Action of March 3, 2004 is acknowledged and has been entered. Previously pending claims 7-37 have been cancelled, claims 1, 2, 5, 6, 38-40, 42-44, 49-51 have been amended and new claims 56-60 have been added. Claims 1-6 and 38-60 are currently being examined.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
4. The following rejections are being maintained:

Claim Rejections - 35 USC 101

5. Claims 2, 5, 6 remain rejected under 35 USC 101 for the reasons previously set forth in the Paper mailed March 3, 2004, Section 5, pages 3-4.

Applicant argues that a second Declaration filed concurrently from Dr. Hauptert states that the concentrations of digoxin evaluated in the two-tailed T test and which was discussed in the prior declaration were micromolar not millimolar concentrations and that the claimed invention is operative.

The argument and Dr. Hauptert's Declaration have been considered but are not found persuasive. As drawn to the apparent typographical error of millimolar versus micromolar, the Declaration is convincing and the first Hauptert Declaration will now be considered in light of the micromolar concentrations actually used..

As drawn to the first submitted Hauptert Declaration, Dr. Hauptert argues that when data points are so near but not directly on the X axis, it is possible that the data points are within the experimental error of the measurement method and therefore are not truly different from zero. Arriving at a determination or clarification of such a situation can be achieved using statistical analysis. Because of the ambiguity of Figure 6, at the highest concentration of digoxin studied, we consulted the raw data in the laboratory notebook and applied statistical analysis to determine the probability that the data points just above the zero lines are in fact different from zero. When the inhibitor was digoxin at 50 and 100 micromolar the results were not statistically significant, indicating that the digoxin values clustered at the highest dose point in Figure 6 are in fact not different from zero inhibition. The argument has been considered but has not been found persuasive as inhibition at 100 micromolar is not disclosed in Figure 6 and it is not clear that how the 100 micromolar point was found, how statistical evaluation was done, how many repetitions, how many datapoints used.

Applicant further argues that the absence of digoxin cross-reactivity for mAB 1-10 is confirmed by fluorescence quenching studies with 10^{-6} and 10^{-5} digoxin. The argument has been considered but has not been found persuasive because the studies are not commensurate in scope with the claimed invention which claims no cross reactivity at 100 micromolar digoxin.

Applicant further argues that the absence of cross-reactivity was also documented by equilibrium saturation binding and points to Parhami-Seren et al, J. Immunol., IDS item. The argument has been considered but has not been found persuasive because a review of the cited reference reveals that the concentrations of digoxin tested were in the nM, not the micromolar range.

All of the arguments and Declarations have been considered but have not been found persuasive for the reasons set forth previously and above and the rejection is maintained. Applicant is invited to submit objective evidence demonstrating that binding of antibody 1-10 and by extension antibody 7-1 (for the reasons set forth previously) are not inhibited by a concentration of digoxin as high as 100 micromolar.

Claim Rejections - 35 USC 112

6. Claims 2, 5, 6 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the Paper mailed March 3, 2004, Section 6, page 3.

Applicant argues that the invention is operative for the reasons set forth above. The arguments have been considered but have not been found persuasive for the reasons set forth above.

Claim Rejections - 35 USC 102

7. Claim 39 remains rejected under 35 USC 102(b) for the reasons previously set forth in the Paper mailed March 3, 2004, Section 8, page 5.

Applicant argues that Lin et al injected Balb/C mice with a ouabain-BSA conjugate and spleen cells from mice showing the "highest titer against ouabain-BSA were selected for fusion. Clearly Lin et al disclose a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain-BSA, not binding specificity for ouabain. The argument has been considered but has not been found persuasive because Lin et al specifically teach, in a competition assay that both antigen and antigen-enzyme conjugate (which is a ouabain-carrier complex) compete for binding to the primary ouabain antibody in the plate (see p. 132, col 2). Clearly, the prior art antibody binds to both free antigen and ouabain-carrier complex.

Applicant further argues that Lin et al do not teach that the monoclonal antibody has binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex. The argument has been considered but has not been found persuasive for the reasons set forth above and further, it is noted that Applicant is arguing limitations not recited in the claim as currently constituted.

Claim Rejections - 35 USC 103

8. Claim 39 remains rejected under 35 USC 103 for the reasons previously set forth in the Paper Mailed March 3, 2004, Section 9, pages 5-6.

Applicant points to arguments submitted to the Office on December 24, 2003. In particular, in said arguments Applicant argued that even if the antibody produced by combining the references produced an antibody that binds to an epitope on ouabain, it does not do so with specificity. The argument has been considered but has not been found persuasive because if an antibody binds to an epitope on a protein it does indeed bind to it with specificity. In particular, the specification teaches, at page 8, lines 13-15, that "binding specificity" is intended to mean "epitopic specificity". The reasons why Applicant states that if an antibody binds to an epitope on ouabain, it does not do so with specificity are unclear. Clarification is requested.

Applicant further argues that in order to produce a novel monoclonal antibody that has binding specificity that is not inhibited by about 100 micromolar of digoxin, Applicants had to develop a novel method to do so and the combined teachings of the references do not teach how to produce a monoclonal antibody to ouabain that is not inhibited by about 100 micromolar of digoxin. The combined references do not use the novel method disclosed in the Application. The argument has been considered but has not been found persuasive because the claim

is not drawn to a monoclonal antibody that is not inhibited by 100 micromolar digoxin.

New Grounds of Rejection

9. The specification is objected to and claims 2, 5, 6, 41-43, 45-48, 49-55, 57-59 are rejected under 35 U.S.C. 112, first paragraph essentially for the reasons previously set forth drawn to the rejection of claims 2, 5, 6, 41-43, 45-48, 53-55 in the Paper mailed March 3, 2004, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

Applicant argues that a Statement under 37 CFR 1.805(a) was submitted on December 24, 2003 in order to overcome the rejection and the pertinent paragraph is reiterated. The argument has been considered but has not been found persuasive because a review of the paper submitted December 24, 2003 and the pertinent paragraph reveals that the statement is drawn to written notification of the USPTO during pendency of the subject application, application for reissue patent or reexamination proceedings, upon notification to Applicant that samples cannot be furnished or that deposit has been contaminated, that samples cannot be furnished or that deposit has been contaminated. Further, the statement continues that a replacement or supplement of the deposit will be made if necessary, which is governed by the same considerations governing the need for making an original deposit under the provisions set forth in 37 CFR 1.802(b). The statement appears to be limited to circumstances drawn only to pendency of the subject application, application for reissue patent or reexamination proceedings. This does not meet the

Deposit requirements. The statement cannot be limited only to pendency of the subject application, application for reissue patent or reexamination proceedings. The arguments have been considered but have not been found persuasive and the rejection is maintained. It is noted that as set forth previously, an affidavit or declaration stating that the deposit will be replaced if viable samples cannot be dispensed by the depository is required.

10. Claims 1, 3-4, 38 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a monoclonal antibody or an antibody binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain carrier complex which is not inhibited by a concentration of digoxin as high as 100 micromolar has no clear support in the specification and the claims as originally filed in the absence of limitations drawn to antibody 7-1, 1-10. Applicant points to page 22, lines 18-20 and Table 1 of the specification for support of the newly added limitations. However, a review of the specification discloses support for three antibodies, antibodies, 5A12 (which has been shown to be inhibited by concentrations of digoxin greater than 25 micromolar), 7-1 and 1-10 which bind Oua-BGG whose binding could not be inhibited with concentrations as high as 100 micromolar of free digoxin. The suggested support has been considered but is not persuasive because, in the absence of the limitations drawn to antibodies 7-1 and 1-10, no support is found for the broadly worded claims drawn to any monoclonal antibody or antigen binding fragment thereof that binds ouabain but is not inhibited at said concentration, no support for the broadly worded claims drawn to any monoclonal antibody or antigen binding thereof that binds to the ouabain component of a ouabain-carrier complex and is not inhibited at said concentration

of digoxin. The subject matter claimed in claims 1, 3-4, 38 broadens the scope of the invention as originally disclosed in the specification.

11. Claims 40-44 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitations of binding of a monoclonal antibody or an antibody binding fragment thereof having binding specificity for ouabain and for the ouabain component of a ouabain carrier complex which is not inhibited by a concentration of digoxin as high as 25 micromolar has no clear support in the specification and the claims as originally filed. Applicant points to Table 1 and Figure 3 of the specification for support of the newly added limitations. However, a review of the Figure 3 discloses support for inhibition of antibody binding to ouabain-BGG by approximately 10^{-5} micromolar Digoxin for three antibodies, antibodies, 5A12, 7-1 and 1-10. Further, a search of the specification did not reveal any statement drawn to concentrations "as high as 25 micromolar". The subject matter claimed in claims 40-44 broadens the scope of the invention as originally disclosed in the specification.

12. Claims 56, 60 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a monoclonal antibody or an antibody binding fragment thereof having binding specificity for ouabain and the ouabain component of a ouabain carrier complex has no clear support in the specification wherein said binding is not inhibited by a concentration of digoxin as high as 50 micromolar has no clear support in the specification and the claims as originally filed in the absence of a limitation drawn to antibody 8E4. Applicant points to page 32, lines 5-7 and 15-16 as well as to Figure 6 for support for the newly added limitations. However, the

support has been considered but has not been found persuasive because a review of page 32 lines 5-7 reveals support for only one stable clone out of many that bound to immunization complex, mAb 84E which binds to Oua alone, and page 32, lines 15-17 reveals that neither digoxin nor gitoxin inhibited 8E4 binding to Oua-BGG at concentrations as high as 50 micromolar. Thus the newly added limitation, in the absence of reference to 8E4 represents new matter. The subject matter claimed in claims 56 and 60 broadens the scope of the invention as originally disclosed in the specification.

13. Claim 39 is rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claim 39 is drawn to a monoclonal antibody produced by a method of making a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and which does not cross react with digoxin, comprising immunizing a mammal with ouabain bound to an antibody which has binding specificity for a glycoside. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that “[a] written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as “vertebrate insulin cDNA” or “mammalian insulin cDNA” without more, is not an adequate written description of the

genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that “naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.” Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. “A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.” Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that “the written description requirement can be met by ‘show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristicsi.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.’ ” Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product to make a particular product.

Thus, the instant specification may provide an adequate written description of the antibody which has binding specificity for a glycoside useful in the method to make a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and which does not crossreact with digoxin, per Lilly by structurally describing a representative number of said antibodies which have binding specificity for a glycoside that when bound to ouabain make antibodies having specificity for ouabain and which do not crossreact with digoxin or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe even a single antibody which has binding specificity for a glycoside that when bound to ouabain makes antibodies having specificity for ouabain and which do not crossreact with digoxin in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of even a single antibody which has binding specificity for a glycoside that when bound to ouabain makes antibodies having specificity for ouabain and which do not crossreact with digoxin, nor any physical or chemical characteristics of even a single antibody which has binding specificity

for a glycoside that when bound to ouabain makes antibodies having specificity for ouabain and which do not crossreact with digoxin nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single antibody which has binding specificity for a glycoside, anti-digoxin 26-10 mAb, which when bound to ouabain and used as an immunogen produces antibodies which cross react with digoxin at greater than 25, 50, 70 micromolar concentrations, none of the produced antibodies have been shown to “not crossreact with digoxin”, and thus this does not provide a description of antibody which has binding specificity for a glycoside that when bound to ouabain makes antibodies having specificity for ouabain and which do not crossreact with digoxin that would satisfy the standard set out in Enzo.

The specification also fails to describe antibody which has binding specificity for a glycoside that when bound to ouabain makes antibodies having specificity for ouabain and which do not crossreact with digoxin by the test set out in Lilly. The specification does not describe even a single antibody which has binding specificity for a glycoside that when bound to ouabain makes antibodies having specificity for ouabain and which do not crossreact with digoxin. Therefore, it necessarily fails to describe a “representative number” of such species. In addition, the specification also does not describe “structural features common to the members of the genus, which features constitute a substantial portion of the genus.”

Thus, the specification does not provide an adequate written description of the antibody which has binding specificity for a glycoside that when bound to ouabain makes antibodies having specificity for ouabain and which do not

crossreact with digoxin that is required to practice the claimed invention. Since the specification fails to adequately describe the product required to produce the claimed antibody, it also fails to adequately describe the synthetic cross-linker protein.

14. Claims 38, 44, 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that implicit in the recitation of a "pharmaceutical" composition is the *in vivo* use thereof for treatment.

The claims are drawn to pharmaceutical compositions comprising monoclonal antibodies or antigen binding fragments thereof having binding specificity for ouabain and for the ouabain component of a ouabain-carrier complex wherein binding is not inhibited by a concentration of digoxin as high as 25/50/100 micromolar. The specification teaches that "in mammals, ouabain (Oua) and/or ouabain-like compounds (OLC) are believed to play a role in the regulation of sodium balance, arterial pressure and vascular smooth muscle tone under normal circumstances and have a pathophysiologic role in common clinical disorders such as hypertension, pregnancy-induced hypertension, cardiac failure, salt sensitivity, chronic renal failure and cardiomyopathy (p. 1, lines 17-21). The availability of specific molecular probes and reliable methods of detecting and measuring endogenous or exogenous Oua is the prerequisite to successfully investigating these issues (p. 2, lines 1-4). The instantly taught antibodies can be used in a method of treating cardiac glycoside toxicity in a mammal comprising

administering a therapeutically effective amount of a monoclonal antibody having specificity for Ouabain (p. 6, lines 15-19), and also treating Ouabain- or OLC-associated hypertension (p. 6, lines 25-27). The specification further teaches that from the clinical point of view, OLC has been implicated in the pathophysiology of human hypertension and congestive heart failure. Patients with these disorders, who will be subjects of clinical studies to verify a role for OLC, are often treated with digoxin. Thus the availability of monoclonal antibodies described herein allow study of patients to verify a role for OLC, even if they are treated with digoxin (p. 27, lines 22-29). The specification further teaches that the monoclonal antibodies described can provide more specific molecular probes to assess the putative role of endogenous ouabain in mammalian physiology and the pathophysiology of the prevalent human cardiovascular diseases, hypertension and congestive heart failure (p. 28, lines 1-10). In one embodiment, the present invention relates to a method of treating cardiac glycoside toxicity in a mammal comprising administering a therapeutically effective amount of a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain (p. 16, lines 4-14). The specification exemplifies monoclonal antibodies that distinguish between related digitalis glycosides (see Example 1) and the determination of level of HIP in human serum (see Example 2).

One cannot extrapolate the teaching of the specification to the enablement of the claims because Parhami-Seren et al (J. Immunol., 1999, 153:4350, IDS item) whose authors include all of the inventors of the instant application, specifically teach that, at the time the invention was made that "in mammals, Ouabain and OLC **may** (emphasis added) play a role in the regulation of sodium balance, arterial pressure and smooth muscle tone and have a pathophysiologic role in common

clinical disorders. Two major issues that need to be clarified are (a) the source(s) of Oua and OLC molecules found in humans and animals and (2) the actual function of Oua or OLC *in vivo* as a regulator of cardiovascular physiology. The availability of specific molecular probes and reliable methods of detecting and measuring endogenous or exogenous Oua is a prerequisite to successfully investigating these issues (para bridging pages 4363-4364). Given the teaching set forth in the specification as set forth above and the teaching of Parhami-Seren et al, it is clear that at the time the invention was made, the roles, if any of ouabain and OLC in human disease was in fact not known. Further, the inventors of the instant invention have made it very clear that the antibodies claimed herein and in the post-filing reference that the claimed antibodies are useful, in particular, to study patients in order to determine the roles of these molecules in human disease. Given that it was unknown what role in fact was played by these molecules, one could not predict and no one of skill would believe it more likely than not that the claimed invention would function as contemplated or implied as a pharmaceutical composition. It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification

would need more detail as how to make and use the invention in order to be enabling.”

Given the uncharacterized nature of the relationship of ouabain to disease, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

15. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a monoclonal antibody produced by a method of making a monoclonal antibody or antigen binding fragment thereof having binding specificity for ouabain and which does not cross react with digoxin comprising immunizing a mammal with ouabain bound to an antibody which has binding specificity for a glycoside.

The specification teaches a single antibody which has binding specificity for a glycoside, anti-digoxin 26-10 mAb, which when bound to ouabain and used as an immunogen produces antibodies which cross reacts with digoxin at greater than 25, 50, and 70 micromolar concentrations (for the reasons set forth previously and above).

One cannot extrapolate the teaching of the specification to the enablement of the claims because although the specification teaches that the invention relates to monoclonal antibodies, i.e. 1-10, 5A12, 7-1, 8E4 or antigen binding fragments

thereof having binding specificity for ouabain, wherein the antibody or antigen binding fragment does not crossreact with digoxin (p. 2, lines 18-20), the exemplified antibodies produced by the exemplified process cross-react with digoxin. The specification further teaches that the advantage of these monoclonal antibodies is that they do not cross react with digoxin, the primary cardiac glycoside used in clinical practice. Thus, the monoclonal antibodies described provide more specific molecular probes to assess the putative role of endogenous ouabain in mammalian physiology and the pathophysiology of the prevalent human cardiovascular diseases, hypertension and congestive heart failure. However, as set forth above, each of the antibodies produced by the claimed process cross-reacts with digoxin. The specification teaches no antibodies with binding specificity to a glycoside that would function as claimed, provides no teachings on how to make said antibody to a glycoside that would function as claimed. Given the teaching in the specification, it is clear that the production of a monoclonal antibody that binds to ouabain but does not cross react with digoxin is an unpredictable art since Applicant has apparently been unable to produce the claimed product using any process.

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict how to make claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

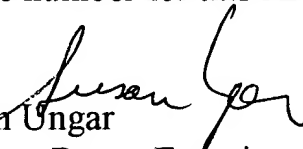
16. No claims allowed.

17. All other objections and rejections recited in the Paper mailed March 3, 2004 are hereby withdrawn.

Art Unit: 1642

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.


Susan Ungar
Primary Patent Examiner
July 1, 2005